How are pregnant women vulnerable research participants?

Wild, Verina

Abstract: Despite the attempts to promote the inclusion of pregnant women into clinical research, this group is still widely excluded. An analysis of the "vulnerability of pregnant women" that questions deeply internalized stereotypes is necessary for finding the right balance in the protection of pregnant women as research participants. Criticism of the traditional account of vulnerability will lead to an alternative that focuses on situations rather than groups and on the obligations of responsible parties. The paper adds to the current general discussion of vulnerability and at the same time addresses the specific problem of drug treatment during pregnancy.

DOI: https://doi.org/10.2979/intjfemappbio.5.2.82

Akzeptiertes Manuskript zu:

Wild, V. (2012): How are pregnant women vulnerable research participants?.
International Journal of Feminist Approaches to Bioethics 5(2): 82-104

Dr. med. Verina Wild
Oberassistentin und stellvertretende Direktorin
Institut für Biomedizinische Ethik
WHO Collaborating Centre
Universität Zürich
Pestalozzistr. 24
CH-8032 Zürich
Tel: +41 44 634 8371
Fax: +41 44 634 8389
wild@ethik.uzh.ch
www.ethik.uzh.ch/ibme

HOW ARE PREGNANT WOMEN VULNERABLE RESEARCH PARTICIPANTS?

VERINA WILD

Abstract

Despite the attempts to promote the inclusion of pregnant women into clinical research, this group is still widely excluded. An analysis of the "vulnerability of pregnant women" that questions deeply internalized stereotypes is necessary for finding the right balance in the protection of pregnant women as research participants. Criticism of the traditional account of vulnerability will lead to an alternative that focuses on situations rather than groups and on the obligations of responsible parties. The paper adds to the current general discussion of vulnerability and at the same time addresses the specific problem of drug treatment during pregnancy.

Introduction

Despite the attempts to promote the inclusion of pregnant women in clinical research, this group is still widely excluded and thus hindered in benefiting from medical progress (Lyerly, Little, and Faden 2009). There are two interconnected reasons why pregnant women continue to be excluded from clinical trials. First, the traditional background assumptions associated with pregnancy, pregnant women, and the fetus still involve a harmful separation of woman and fetus that in some cases leads to an unbalanced prioritization of fetal needs. The second reason is that pregnant women are included in the category of "vulnerable groups." It is therefore essential to examine and reassess the general understanding of "pregnancy" and "vulnerability" in order to

develop an ethically sound approach to the question of pregnant women's participation in clinical trials. Appropriate safeguards—for example in order to avoid fetal harm—can only be implemented once this reassessment is convincing and successful.

Part I describes how pregnant women were first excluded from participation in clinical trials and how then regulatory bodies allowed their inclusion again. Voices from Germany will be used as examples showing the problems of linking vulnerability to the decision-making capacity of pregnant women. The main point is to show that there is still no clarity about the concept of the vulnerability of pregnant women.

In Part II, the prevalent "traditional" account of vulnerability—which is connected to voluntary informed consent—will be explored and rejected for pregnant women. In parallel, the understanding of pregnancy is reassessed and the concept of the "double unit" is developed.

In Part III, an alternative account of vulnerability, understood as exposure to increased likelihood of harm, will be developed, based on a) the insights gained in the previous sections; and b) selected elements of earlier works on vulnerability. This will lead to the following approach to recognition of special vulnerabilities, such as those that may arise in pregnancy: *In the context of biomedical research, vulnerability arises in those situations which might lead to an increased likelihood of harm for some potential research participants. It is the obligation of those responsible for clinical trials to identify these situations that generate vulnerability and to develop appropriate safeguards against the increased risk of harms resulting from those situations*. This alternative account of vulnerability requires three central elements: 1) vulnerabilities are context-dependent, dynamic, and situational; 2) for greater clarity and to avoid wrongful labeling, situations with an increased likelihood of harm should be clearly identified; and, 3) the detection of such situations must result in defining the subsequent obligations of those who are responsible for the trial.

This paper will discuss the case of clinical research on pregnant women in order to enrich the ongoing conceptual discussion in research ethics about "vulnerability."

Pregnant women as research participants and the open question of vulnerability

In 1954, the German company Chemie Grünenthal GmbH developed the drug Contergan® (Thalidomide) and sold it to a total of forty-six countries. At that time, there was no regulatory requirement for clinical trials prior to the approval of drugs. In the early 1960s, physicians started detecting malformed extremities of children born to women who had taken Contergan® during pregnancy (Lenz et al. 1962; Marquardt 1994; McBride 1961). Trading of the drug was stopped by November 1961.

On the one hand, the so-called "fall of man after a careless use of therapeutic drugs" (Müller-Oerlinghausen 2005, 33) led to the groundbreaking implementation of regulations for general pharmaceutical trials. On the other hand, this incidence caused a major turn concerning drug therapy during pregnancy: "Then came the Thalidomide catastrophe—and suddenly the world was aware that the human embryo was not sequestered in an impervious maternal body where it was shielded from all but genetic harm" (Wilson 1979, 205). From then on, a widely practiced and legally mandated *exclusion* of pregnant women from clinical trials (FDA 1977) took place.

However, this mandated exclusion led to therapeutic difficulties during pregnancy (e.g., Caschetta, Chavkin, and McGovern 1993; Scott and Purohit 1989). Increasingly it was understood that the lack of evidence to support therapeutic decisions in caring for pregnant women was due to the ongoing exclusion of pregnant women from clinical trials. Hence, the argument for including pregnant women in clinical trials accelerated in the United States in the early 1990s (Caschetta, Chavkin, and McGovern 1993; Merkatz et al. 1993). From an ethical perspective, the notion of "vulnerability" of pregnant women in the context of clinical research was rejected, because there was no reason to believe that pregnant women could not make

autonomous decisions or that pregnant women were particularly prone to being exploited (Anderson 1994; Macklin 1994; Mastroianni, Faden, and Federman 1994).

As a significant result of that debate, since 2001 various regulations have been changed to mandate the *inclusion* of pregnant women in clinical trials under certain circumstances. Among these were the U.S. regulation (HHS 2009), the "Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research" of the Council of Europe (Council of Europe 2005), and the CIOMS guidelines (CIOMS 2002). Whereas the Council of Europe and the CIOMS do not clarify the concept of vulnerability in the context of pregnancy, the influential U.S. regulations explicitly label pregnant women as a vulnerable population: "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects" (HHS 2009).

Despite the regulatory mandates to include pregnant women into clinical research, little has changed. Even for relatively common conditions Cochrane Collaboration Reviews conclude that there is insufficient data to recommend any specific drug treatment, either due to small sample sizes (e.g., urinary tract infections: Vazquez and Abalos 2011), because no randomized clinical trials exist (e.g., deep vein thrombosis: Che Yakoob et al. 2010), or because there is a general lack of high-quality evidence to back up any advice (e.g., nausea and vomiting: Matthews et al. 2010). In total, only about a dozen drugs have been approved for use during pregnancy, and more than half of these drugs have had their approval rescinded (Haire 2001). Because of the lack of evidence about safe and effective drug treatments during pregnancy, a recent "second wave" of bioethicists has criticized the ongoing exclusion of pregnant women from clinical trials (Lyerly, Little, and Faden 2008; Lyerly, Little, and Faden 2009).

The example of Germany

It is not only in official regulations that one can find the labeling of pregnant women as a vulnerable group. The public debate in Germany serves as an example that shows how vulnerability is routinely attributed to pregnant women and that it is widely connected to the decision-making capacity of pregnant women.

In Germany, no national law explicitly regulates research on pregnant women. Thus, the above-mentioned Additional Protocol to the European Convention is currently the only instrument regulating clinical trials during pregnancy. Notwithstanding, pregnant women are—as in many other countries—frequently excluded from clinical research. In 2003, German bioethicists raised the question of whether the current exclusion of pregnant women from clinical trials is an appropriate protection or whether it is in fact a form of paternalistic and harmful overprotection (Biller-Andorno and Wild 2003a; 2003b). Leading reproductive toxicologists responded to the bioethicists' concerns with extensive criticisms and concluded that a liberalization of the exclusion of pregnant women from clinical trials was not necessary or desirable (Schaefer, Spielmann, and Vetter 2004). From their point of view, collecting retrospective data was sufficient for the improvement of medical treatment during pregnancy and feminist claims could not justify research on pregnant women: "It is not permissible to make a pregnant woman responsible for an experiment which she cannot judge sufficiently. The reference to the argument of equality . . . seeks to justify the potentially risky testing of questionably beneficial drugs with an emancipatory pretension" (A166, my translation).

This quotation raises important issues for the question of vulnerability. In their first argument, the authors take away pregnant women's right to decide whether to participate in trials, claiming that they cannot sufficiently evaluate an experiment. Even if the authors do not explicitly say so, the implication is that pregnant women lack the capacity to judge a complex situation adequately. Thus, the authors distinguish pregnant women and their decision-making

capacity from that of nonpregnant women and men, who unquestionably have the right to decide upon participation in a clinical trial.

The author's second argument refers to gender justice. In their paper, Biller-Andorno and Wild had attempted to initiate a debate on whether the exclusion of pregnant women is overprotective and thus harmful (Biller-Andorno and Wild 2003a). But Schaefer, Spielmann, and Vetter rejected this first attempt at critically assessing the status quo in Germany, dismissing it on the grounds that gender equity ("an emancipatory pretension") is secondary to protecting pregnant women against the possible risks of clinical trials.

In this short quotation, one can see the strong reluctance to acknowledge pregnant women as competent and autonomous decision makers and to acknowledge the call for equity in the case of clinical research. Instead, the dominant concern was to protect pregnant women (or possibly more importantly, the fetus) from any kind of risk resulting from clinical trials. This quotation is an excellent example to show how the general labeling of pregnant women as a "vulnerable group" needing protection from clinical research precludes further discussion and possible improvement in the area of therapeutic evidence during pregnancy.

A German bioethicist argued similarly in an expert opinion of the federal Enquête Commission "Ethics and Law in Modern Medicine":

> Research on pregnant women that risks damage to an embryo cannot be justified by arguments about the autonomy of pregnant women and knowledge gaps concerning teratogenicity of drugs alone. It is impermissible to shift the responsibility for the risk-benefit-assessment from the researchers to the research participants. In contrast to the researchers, the research participants cannot adequately judge the consequences of an experimental therapy. (Bobbert 2004, 56, my translation)

Like Schaefer, Spielmann, and Vetter, Bobbert refers to the autonomy and decision-making capacity of pregnant women and explicitly states that pregnant women cannot adequately judge

the situation. Thus she also distinguishes pregnant women from non-pregnant women or men by saying that in this special case the potential participants cannot judge the potential risks. The line of argumentation is surprising, since it should never be the participant's responsibility to perform the risk–benefit assessment prior to a clinical trial in the first place. Instead, it is the obligation of researchers and Institutional Review Boards (IRBs) to assess the risk–benefit ratio and to inform the participant, who then makes her informed choice. This is the standard procedure, which should apply to pregnant or non-pregnant individuals alike. To make an exception for pregnant women and to protect them from any possible risk means to attribute a vulnerability to pregnant women (or their fetus), which the authors justify by ascribing an insufficient *decisional capacity* to pregnant women.

The categorical exclusion of pregnant women from clinical trials remains unquestioned in Germany, as examples from the academic literature and the media illustrate. In a study on antibiotics in pregnancy the author claimed, “It goes without saying that clinical trials on pregnant women are forbidden for ethical reasons” (Imhof 2005, 5, my translation). During the H1N1 epidemic in 2009, journalists wrote: “Vaccination . . . has not been tested on pregnant women at all. Clinical research on pregnant women is classified as unethical” (Winkelheide 2009, my translation); and “But pregnant women are excluded from this test phase, as they are from any other clinical trial” (Langemak 2009, 1, my translation). A section of the German Health Ministry wrote on their homepage, “Clinical trials prior to the approval for H5N1 vaccination have not been conducted on pregnant women for ethical reasons” (Paul-Ehrlich-Institut 2009, my translation).

These remarks show how readily accepted the exclusion of pregnant women seems to be for unspecified “ethical reasons.” If no fundamental discussion takes place regarding underlying background assumptions about the “vulnerability” of pregnant women and the concept of “pregnancy,” then little will change in the future. An explicit analysis that is able to question

deeply internalized stereotypes is necessary in order to find the right balance between over- and underprotection of pregnant women in the context of clinical trials. In the next section, therefore, I will further elucidate the underlying concepts.

The "traditional" understanding of vulnerability

Which arguments support the classification of pregnant women as vulnerable? In order to answer this question it is necessary to know what is generally understood as "vulnerability" in the context of biomedical research, independent of pregnant women. Unfortunately, this is the very question that leads to disagreement (Coleman 2009; Hurst 2008; Levine et al. 2004; Ruof 2004). However, in many accounts of vulnerability, as in the U.S. guidelines or in the Declaration of Helsinki, two criteria that are connected to voluntary informed consent are used to justify special protection for certain groups or populations: impaired decision-making capacity, and risk of exploitation.[1] Both criteria imply that these groups are vulnerable to greater harm through participation in clinical trials than other nonvulnerable groups. There are voices that criticize this account of vulnerability (Coleman 2009; Hurst 2008; Kipnis 2006; Luna 2009; Macklin 1994; Wild 2010), but it is nevertheless far from resolved. This "traditional view" is, in fact, still prevalent and effective, and should therefore be evaluated regarding the special case of pregnant women. An explicit discussion and criticism of this understanding is useful in order to develop a well-balanced understanding of vulnerability.

Decisional incapacity

Assumed limited capacity for decision making is a dominant argument for special protection and—as we have seen—even exclusion of the group of pregnant women from clinical trials. What needs to be explained is whether the assumed limitation is in the capacity of pregnant women to make decisions, or in the capacity of the fetus. While Beauchamp and Childress argue in their newest edition of *Principles of Biomedical Ethics* that pregnant women

are not vulnerable per se (Beauchamp and Childress 2009, 254), in the newly added chapter on vulnerability the fetus is explicitly mentioned as a prototypical example of a member of a vulnerable group. Taking up this division between pregnant woman and the fetus, the argument of limited capacity of decision making could be understood in the two following ways:

Possibility 1: The fetus cannot give consent. This leads to the vulnerability of pregnant women as research participants.

Possibility 2: The pregnant woman's decision-making capacity is impaired. This leads to the vulnerability of pregnant women as research participants.

I will demonstrate that neither of these versions of vulnerability is sound. It is inappropriate to separate the pregnant women and the fetus as single units of concern. An explicit understanding and explanation of the concept of "pregnancy" and "pregnant women" is essential in order to continue with an appropriate discussion of vulnerability in the context of clinical research for the special case of pregnant women.

Possibility 1: Because a fetus cannot give consent, we might infer an ethical imperative for third parties to protect the fetus from harm. If so, we must clarify whether it is appropriate to examine the decision-making capacity of the fetus alone as if he or she existed as a person, and if so, who the relevant third party is to make a substituted judgment. If the fetus is regarded as an individual "person," then an individual moral status with individual rights, for example equal to children's rights, is plausible.

In line with an extensive body of feminist writings, I criticize this approach and argue for a nonisolated and nonindividualized position of the fetus as being an integral part of the pregnant woman's body. The ongoing generalized exclusion of pregnant women from clinical trials shows that it is necessary to reintroduce the central insights of the feminist view on the concept of pregnancy and consider them anew in the context of clinical research.

The problematic "fetal individualization" and separation from the mother has been described as a consequence of technological innovations, namely *visualization* in medicine (see Duden 1994; Meredith 2005; Schindele 1990; Schneider 1995). Wiesemann emphasizes that it was in great part the photographer Lennart Nilsson who created the picture of the fetus as an independent individual by publishing his artificially manipulated pictures in the 1960s (2006, 77–78, referring to Nilsson 1965). By using *dead* fetuses, he produced the putative and illusory idea of an independent unborn child. The visualization of the fetus as an individual is hence an artificial construct that leads to a one-sided focus on the fetus. This occurred together with an emphasis on fetal rights on the one hand and the anonymization of the "surrounding" mother and loss of sight of women's rights on the other (Schindele 1990; Schneider 1995; Stormer 2003).

What does this mean for the personal status and moral rights of a fetus? In relation to the debate on abortion, Sherwin presents two lines of argument. She differentiates between feminist and nonfeminist argumentation. The former puts the woman in the center of attention; the latter focuses on the moral status of the fetus:

> The most obvious difference between feminist and non-feminist approaches to abortion can be seen in the relative attention each gives to the interests and experiences of women in its analysis. Feminists consider it self-evident that the pregnant woman is a subject of principal concern in abortion decisions. In most non-feminist accounts, however, not only is she not perceived as central, she is rendered virtually invisible. Non-feminist theorists, whether they support or oppose women's right to choose abortion, focus almost all their attention on the moral status of the developing embryo or the fetus. (Sherwin 1998, 375)

Sherwin makes this distinction in the context of abortion, which may differ from the case of clinical trials. In the case of abortion, the concern is the woman's decision whether to end her pregnancy; in the case of research, frequently the women concerned want to bring their pregnancies to term and most likely have a strong interest in protecting their fetuses and future

children from harm. Sherwin's distinction is nevertheless helpful for the case of pregnant women's decision-making capacity in the context of clinical research because it emphasizes the above-mentioned problematic individualization of the fetus that leads to the central questioning of its moral status. The feminist view focuses on the decisional capacity of the woman and rejects a separation of woman and fetus as two parties with competing rights.

A fitting concept is thus to conceive of woman and fetus categorically as a "double unit," consisting of two parts, the woman and the unborn child, and for which the woman is the only *person* who can and should make a decision. The bodily connectedness between mother and fetus and the resulting intimate relation constitute a unique bond. Such a close relation in which one part (the mother) provides the necessary condition for the coming into existence of the other (the fetus) does not exist in any other form of human relationships. All the woman's decisions affect her as the "double unit." Mackenzie puts the uniqueness of the double unit into words:

> The experience of pregnancy, particularly in the early stages, is unique in the sense that it defies a sharp opposition between self and other. . . . The foetus, to the extent that it is experienced as part of the woman's body, is also experienced as part of her self, but as a part that is also other than herself. . . . It is a being, both inseparable and yet separate from her, both part of and yet soon to be independent from her. (Mackenzie 1992, 148)

Because the fetus is part of the double unit for which the woman has the decisional capacity, it is not appropriate to speak of the fetus as an isolated individual. Its status is therefore not comparable to any other individual incapable of making autonomous decisions, who might deserve *individualized* protection from third parties. Following this line of argument, possibility one (*The fetus cannot give consent. This leads to the vulnerability of pregnant women as research participants)* can be rejected.

Possibility 2: According to both Schaefer and Bobbert (see above), pregnant women *cannot decide* about the risks of trials, and given the risks of potential harms to the fetus, on their

account trials are not morally justifiable. For them, the argument of the decisional incapacity of the woman seems to rule out the possibility of clinical trials with pregnant participants altogether. But why should a woman, who is principally capable of making her own decisions—even in risky situations—not have the ability to do so *during pregnancy*? A few studies have investigated the decision-making capacity of pregnant women (Dorantes, Tait, and Naughton 2000; Rodger et al. 2003). These studies show that there can be certain situations, as when the woman feels strong pain or during labor and childbirth, when pregnant women might experience limited decision-making capacity. Further, situations might occur when the decision-making capacity is impaired due to psychiatric conditions, drug abuse, or medical conditions like coma.[2] But there is no reasonable argument to conclude that *pregnancy itself* leads to an impaired decision-making capacity of the woman. Interviews show that the feeling of "double responsibility" sometimes leads to even more reflective and prudential decision making (Wild 2010, 135). Hurst therefore rightly calls the classification of pregnant women as vulnerable on the grounds of an impaired decision-making capacity "stereotyping and insulting" (Hurst 2008). From an empirical point of view, but also from a theoretical standpoint, there are no reasons to conclude that just because a woman is pregnant, her decision-making capacity is impaired. Possibility two (*The pregnant woman's decision-making capacity is impaired. This leads to the vulnerability of pregnant women as research participants)* can therefore also be rejected.

Both possibilities one and two have been rejected. As a conclusion, it is not possible to classify pregnant women as a vulnerable group on the grounds of a generalized decisional incapacity. Instead, some situations have been identified that might lead to a certain vulnerability. Despite this finding, however, an alternative understanding of vulnerability has not been developed. Nor is the description of a double unit explicit enough concerning whether anyone should feel responsible for fetal well-being in the context of clinical research, and if so,

who and why. Both issues—an alternative understanding of vulnerability, and responsibility for the fetus—will be taken up later in this paper.

Higher risk of exploitation

Increased risk of exploitation is another classic criterion for vulnerability and is also connected to informed consent. It might apply to people who cannot decide voluntarily for or against participation in a clinical trial, if they are under constraints or external pressure to decide in favor of participation. In principle, all the reasons *irrespective of pregnancy* that one can think of as leading to a higher risk of exploitation can also occur during pregnancy: language difficulties, poverty, low formal education, or specific hierarchical constellations. But these reasons for vulnerability are—like impaired decision-making capacity—prevalent only in certain situations and in certain contexts. They are clearly not generalizable for all pregnant women. Situations that occur only during pregnancy might also lead to a higher risk of exploitation, for example, in situations in which the pregnant woman feels moral pressure to do what is best for her child. Findings from a British interview study (Mohanna 1997) as well as results from my prior research support this claim (Wild 2010). In qualitative interviews, I asked thirty pregnant women whether they would participate in a trial that tests a new hormone that might prevent preterm birth even though the women will probably suffer from severe nausea. Whereas the women were very reluctant about most other study scenarios (with benefit for themselves), almost all of them readily agreed to participate in such a study for the benefit of the fetus. In many cases, the women emphasized their will and wish to do the best for their unborn child, even if that interfered with their own needs. Hence, in a risky study with great potential benefit for the fetus, some women might overlook or downplay the risks to themselves, but clearly more research is needed on this issue. Thus, studies advertising a substantial benefit for the fetus might lead to potentially exploitative situations, thereby necessitating special safeguards related to this

vulnerability. However, this specific type of vulnerability is, again, *situational*. It is only relevant in the setting of a trial with significant benefits for the fetus and risks to the woman.

So far I have shown that an oversimplified generalization of the group of pregnant women as being vulnerable on the traditional approach has been misleading. It has led to a paternalistic and stigmatizing exclusion from research of the entire group of pregnant women. The aim of this paper is to build on the criticism of the traditional concept of vulnerability in order to develop a more balanced approach and responses to vulnerability. But before moving on to this step, clarification is necessary regarding whether the existence of the fetus—as part of the double unit—has any effect on the ethical evaluation of participation of pregnant women in clinical research.

Responsibility for fetal well-being

If pregnant women can be vulnerable in the context of clinical research—and I will conclude that they can be in certain situations—what role does the fetus play? The concept of a double unit suggests that it is inappropriate to individualize the fetus. It grounds criticism of a one-sided focus on potential fetal harms together with neglect of the harmful consequences this can have, in turn, for the woman. This approach also establishes that the pregnant woman is the *person* who should make the ultimate decisions concerning herself (as the double unit).

However, being characterized as a double unit also implies the trivial insight that pregnant women are different from nonpregnant individuals *because of their pregnancy*. As I will show in the next section, various reasons might lead to a certain kind of vulnerability, *even if* the pregnant woman is seen as a double unit, and a separation of the fetus from her as an independent unit of concern is rejected, and *even if* she is considered to have full autonomy.

Further, just because a separation of pregnant women and fetus is inadequate, this does not mean that all responsibility toward the fetus rests upon the woman. One important insight from the feminist view is that relations matter. In the case of clinical trials it is obvious that the

unique relationship, or bond, between pregnant women and their fetuses matters. But so does the relationship between the father and the pregnant woman (and her fetus), as well as that of the clinical researchers toward her (and her fetus).

Many clinical trials would probably include pregnant women who plan to bring the pregnancy to term. Thus the fetus should be regarded as her (or someone else's) *future child* and that is why its well-being matters morally. As Mackenzie claims, "in a context in which some one or more members of the moral community have decided to take parental responsibility for its [the fetus's] future well-being, it [the fetus] has moral significance by virtue of its relations with her or them" (Mackenzie 1992, 143). If parental responsibility has been established, it is the researchers' duty to respect this and therefore to care for the fetus's well-being.

A researcher who designs a study in which a pregnant woman shall participate must see her as a double unit, that is, neither *only* as a woman or *only* as a fetus, nor *both* as two separate units of concern. If the fetus is harmed, for example because a preterm birth results from a clinical trial, this will affect the woman too. And if a woman suffers from side effects of a drug, for example by developing severe nausea, her fetus will also be affected. The risk–benefit assessment of a trial must consider harm to the woman *in connection to* the fetus and vice versa.

It would thus be laudable to design a study that tests an off-label drug in a randomized clinical trial, which compares two antihypertensive drugs widely used during pregnancy, in pregnant women who suffer from gestational hypertension and are already being treated. Such a study would enhance therapeutic evidence for the use of those drugs during pregnancy and could ultimately lead to official drug approval for use in pregnancy. After being well informed about the potential risks of the trial, it would be the pregnant women's decision whether to participate or not.

But it would not be justifiable to set up a call for healthy pregnant women who want to bring their pregnancies to term to participate in a study that tests Thalidomide. The researcher

would knowingly create a hazard for the *double unit* that would not be outweighed by potential therapeutic benefits. This would clearly be an ill-designed study that would violate a main ethical regulation for clinical research, namely that "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects" (Helsinki Declaration 2008).

In conclusion, the researcher self-evidently has a responsibility toward the well-being of the fetus as soon as parental responsibility might be or has been established. But the fetus can only be considered a part of the woman, who is—after being properly informed—the person with the ensuing right to decide whether or not she wants to participate in the trial.

A balanced application of "vulnerability" in the context of clinical research

In this section I want to show what can be learned from the example of pregnant women for understanding "vulnerability" in the context of clinical research. An appropriate account should be balanced and should prevent an overly permissive attitude, while at the same time it should avoid any kind of victimization, stigmatization, or harmful labeling that would lead to an overly protective stance.

By drawing on elements of seminal works (esp. Hurst 2008; Levine et al. 2004; Luna 2009), I will argue that vulnerability in the context of biomedical research remains a valid concept. However, vulnerability should not be generally assigned to certain groups, as the example of pregnant women has shown. Instead, I suggest a shift of focus away from groups to *situations* that individual participants might find themselves in, and also to the *responsibility of researchers*. Hence, the following approach to understanding special vulnerabilities in biomedical research: *In the context of biomedical research, vulnerability arises in those situations which might lead to an increased likelihood of harm for some potential research participants. It is the obligation of those responsible for clinical trials to identify these situations*

that generate vulnerability and to develop appropriate safeguards against the increased risk of harms resulting from those situations.

It is necessary to specify precisely what this approach means in order to ultimately ensure a balanced protection of individuals. The following central elements of an adequate approach to vulnerability result from my criticism of the traditional account of vulnerability: 1) vulnerabilities are context-dependent, dynamic, and situational; 2) for greater clarity and to avoid wrongful labeling, situations with an increased likelihood of harm should be clearly identified; and, 3) the detection of such situations must result in defining the subsequent obligations of those who are responsible for the trial.

Vulnerabilities are context-dependent, dynamic, and situational

Today, many authors agree that vulnerability in clinical research should be understood as context-dependent and dynamic and not as a static definition aimed at targeting and permanently labeling certain groups (Levine et al. 2004; Luna 2009; Wild 2010). As a dynamic concept, vulnerability is situational and can change as the context and situation change. This calls for context-sensitivity and an explicit description of the given situation.

In the case of pregnant women, context-sensitivity requires explicit clarity about the understanding of the participant, including an understanding of the maternal–fetal relationship. I have treated this topic above and proposed an understanding of the pregnant woman and her fetus as a double unit for which the woman can and should make decisions. A dynamic conception of vulnerability also calls for detecting situations in which an increased likelihood of risk might occur. This will be elucidated in the next section.

A dynamic understanding further suggests that every potential research participant could come into situations with an increased likelihood of harm. This does not weaken the concept of vulnerability. Rather, I argue that researchers or IRBs are thereby forced to carefully examine the context in which the study is taking place and the situation in which the potential study

participant is being placed, in order to detect real and existing vulnerabilities more specifically. Only then can appropriate safeguards be implemented and the balance achieved between too much and too little protection.

Identification of potential situations with an increased likelihood of harm

The context-sensitive understanding of vulnerability entails that the attribution of somebody as *being* vulnerable is inappropriate. Instead, what matters is the surrounding context to which somebody might be vulnerable: persons or entire groups can only come into situations where they become vulnerable *to* certain harms (Coleman 2009; Hurst 2008). To understand that persons can be vulnerable *to* something strengthens the fact that the surrounding—and not the "label"—counts (Kipnis 2006; Luna 2009). It fosters the obligation of those responsible for clinical trials to detect and clearly name the specific situation that brings about possible harms. But how should somebody who is responsible for the conduct of a clinical trial actually identify such situations? Luna's development of "layers not labels" regarding vulnerability is helpful in this regard (Luna 2009). But what Luna explicitly rejects is any form of categorization in order to detect vulnerabilities.

In contrast, I believe that a rough guide outlining where to search for such situations with an increased likelihood of harm would be useful. For this purpose, I appreciate the approach developed by Levine et al. (2004), Hurst (2008), and Coleman (2009). Levine et al. identify three types of research protocols that might deserve special scrutiny. Here, the research situation (and not the potential participant or group) is the center of attention, for example, in the case of testing new drugs or interventions with possible irreversible effects or when there is a credible risk of significant harm. Hurst searches for potential wrongs[3] that could occur while participating in a trial. She develops a four-step approach that includes the search for potential research subjects at risk of being wronged, the identification of subjects who might be more likely to be harmed than others, the question whether the given IRB is among those who share the duty to minimize or

avoid the wrong, and the identification of possible steps to react in an appropriate way. Coleman distinguishes between risk-based, consent-based, and justice-based vulnerabilities (2009). These categories are helpful, but it is important to use them for the identification of *situations* that lead to increased risk of harm rather than vulnerabilities. The latter might again run the risk of labeling groups instead of shifting the focus to the actual situation and the resulting responsibility for the researchers and the IRBs.

The following categories—risk, choice, and injustice—should not be understood as static and exclusive; they can overlap. Hence, these three categories should only serve as the required rough guide in order to better detect situations of increased likelihood of harm.

First, some study designs might show a significantly *unfavorable risk–benefit ratio*, which can lead to situations that render potential participants vulnerable. In such cases, special safeguards can be appropriate. The fact that some interventions and drugs might harm pregnant women and their fetuses significantly more than others might lead to such a significantly increased risk with no justifiable benefit, for example, in the above-mentioned case of a trial testing Thalidomide on healthy pregnant women who want to bring their pregnancy to term. Thus it may well be that some studies justify an adaptation of the study design or even the exclusion of pregnant participants.

One could also find applications of this understanding that would exclude diabetics from a clinical trial. For example, it might be appropriate to adapt a study design or even ban participation for this specific group, if the drug or intervention under investigation could seriously affect the blood glucose level. Unlike pregnant women, diabetics are not traditionally listed as a vulnerable group and yet both might be potentially placed in situations where special protection is justified. This example shows the particular importance of the situation in making members of one group at increased likelihood of harm (i.e., vulnerable) in the context in question.

Hence, even if potential participants capable of giving consent (such as pregnant women or diabetics) are taken seriously as full moral agents whose autonomy is respected and who can participate in decision making, they might still be susceptible to situations where they are rendered vulnerable due to a significantly increased risk when compared to other potential study participants.

Many situations with an increased likelihood of risk of harm are not specific to pregnant women, and can also apply to other persons or groups. It will be difficult to find the appropriate threshold for such an increased level of risk that justifies adaptation of the study design or even exclusion of certain participants. The challenge is to specifically detect and explain situations with such an unfavorable risk–benefit ratio and not to systematically rule out an entire group as potential participants in clinical trials.

Second, a situation of vulnerability connected to *choice* can apply in a range of circumstances. Some people are not as *able* as others to refuse participation in a trial, for example due to coma, intense pain, age (e.g., newborns), or in case of some mental illnesses. Others are not as *free*. This occurs in situations in which adequate freedom to choose is lacking, because participants may be in circumstances that increase the potential for exploitation. This could be the case, for example, when people are in desperate need of treatment and cannot otherwise afford it, in certain hierarchical constellations, or when freedom is limited (e.g., for a prisoner or an asylum-seeker in certain countries). Other situations of exploitation can occur if there is lack of information, a language barrier, or financial incentives.

Searching for vulnerabilities connected to restricted choices calls to mind the traditional understanding of vulnerability. However, that understanding aims at identifying groups that fall under these categories. Identifying *situations* instead of groups focuses attention upon the specific context, and this ultimately leads to a more sensitive and nuanced understanding of the obligations that result for the researcher. Even in the case of an "intrinsically vulnerable" person

like a woman in a coma or a newborn, what should be important for the researcher is the specific situation into which this intrinsically vulnerable person is brought. In examining the situation, questions arise regarding the kind of research being performed, what harm can be done to the potential participant, and—since the research and the researcher are essential elements of the situation examined—which obligations follow from this analysis for the researcher.

Regarding pregnancy, most of these choice-related situations are not pregnancy-specific. However, in the case of pregnant women we have seen that a study with significant expected benefits for the fetus and substantial burden for the pregnant woman might lead to the strong wish to participate in the trial without fully weighing risks and benefits. Such a situation, which might affect a woman's decision making, needs to be detected and appropriate actions have to be taken. This could be, for example, the requirement to assign an independent expert (e.g., a psychologist or clinical ethicist) to talk about the risks and benefits in more detail with the women.

Third, situations creating potential vulnerability should not be understood solely as sporadic or temporary circumstances. Situations that render someone vulnerable could also be due to structural circumstances and systematic disadvantage, for example when certain persons or groups—like the group of pregnant women—are continuously and *unjustly* excluded from meaningful studies. In this situation, a person or group is rendered vulnerable by structural exclusion, which deprives them from participating in the benefits of medical progress. Researchers should then implement safeguards against unjust exclusion, or should at least have to justify why they do *not* include these persons or groups.

Another example of structural injustice includes discrimination against certain persons or groups for the sake of research and with this the perpetuation of their disadvantageous circumstances. If, for example, a study systematically targets only poor or homeless participants, even though the research is not addressed to their needs, potential participants might be brought

into a situation of increased likelihood of harm through the conduct of the trial. Researchers' obligations start with the recognition of this systematic injustice and should lead to a constructive solution, for example ensuring the participation of alternative groups, or changing the design and setting of the trial altogether.

Determining the obligations that result for researchers

The context-dependent approach, with its focus on specific situations, is incomplete without a determination of the obligations of those responsible for setting up a clinical trial. What is essential is the *active role* of the responsible counterpart. Hence, in the context of clinical research, the detection of situations that might lead to vulnerability is most important for those who design and conduct studies, and for those who approve them. For Goodin, recognition that others are vulnerable to one's actions makes one responsible for those who are vulnerable: "It is vulnerability . . . that plays the crucial role in generating special responsibilities" (1985, 107). What matters is the obligation of the responsible others to screen for possible situations where vulnerabilities might occur. Further, it is important to implement the appropriate actions that result once a situational vulnerability has been detected (Step 4 in Hurst's account of vulnerability; Hurst 2008). For example, it does not suffice to automatically exclude participants from clinical research altogether if a possible situation leading to vulnerability is detected. This would easily lead to precisely the sort of unjustified exclusion imposed upon pregnant women (Mastroianni, Faden, and Federman 1994). A focus on the IRB's and researchers' responsibility should foster a differentiated reaction to possible situations of vulnerability. This might necessitate a higher burden of detailed evaluation if special safeguards must be discussed and, when justified, implemented not only for each clinical trial, but potentially for each participant as well.

If, for example, there is reason to believe that the risk of harm from participating in a specific trial is higher for pregnant women (and the fetus) than for others, this would result in

special obligations for those responsible for the trial. This could entail assessing the risk–benefit ratio more specifically, conducting more pretests, and monitoring the women or their fetuses more closely during the trial. It could also mean banning participation for certain trials altogether. This emphasis on responsibility requires researchers and IRBs to specifically explain the given situations and to develop the appropriate safeguards.

Conclusion

By discussing vulnerability and pregnancy in the context of biomedical research, this paper has revealed three main flaws in the traditional account of vulnerability.

First, the traditional strategy of classifying entire groups as vulnerable has proven to be unspecific and harmful. Instead, the focus should be on situations that can lead to vulnerabilities and the resulting obligations for others.

Second, the traditional account of vulnerability that is exclusively connected to voluntary and informed consent was shown to be flawed. This paper suggested that a dynamic approach that takes various situations connected to risk, choice, and justice into account is more suitable.

Third, it is problematic to apply the traditional account of vulnerability to pregnant women. In this special case it was important to revise the understanding and background assumptions of the concept of "pregnancy" and "pregnant women." An appropriate account of vulnerability can be applied only if the special relation between pregnant women and the fetus is understood.

With this more nuanced understanding of vulnerability and pregnancy in mind, current regulatory approaches should be reassessed and, when indicated, revised. The overall aim should be improvement of the currently unacceptable situation concerning therapeutic options during pregnancy.

The alternative account of vulnerability presented here is also helpful beyond the special case of pregnant women, as it assists in identifying vulnerability in certain situations instead of

paternalistically stigmatizing entire groups as incapable of giving consent. Therefore, those responsible for clinical trials can develop specific safeguards and thereby better assume their responsibility. A challenge for future research will be to properly identify situations that involve an "increased likelihood of harm"—thus requiring special safeguards—and to distinguish them from situations that do not. There will likely be complex cases for which it will remain unclear whether they fall under the category of creating vulnerability and whether special safeguards are justified. However, it is promising to pursue this path further, because the focus on ability to freely give consent and on special groups as criteria for determining vulnerability has failed to prove itself a reasonable concept in research ethics.

Acknowledgments

I am grateful to two anonymous reviewers, and to Nikola Biller-Andorno, Agomoni Ganguli Mitra, Jan-Christoph Heilinger, Tanja Krones, Annette Rid, and the editors for their thoughtful and constructive comments on this paper or earlier versions of it. The paper has benefited enormously from their efforts.

Notes

1. See, for example, Helsinki Declaration 2008, 9: "Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence."

2. Situations that influence the decision-making capacity due to exploitation or coercion will be addressed in the next section and will also be taken up again in the last section on an alternative account of vulnerability.

3. Hurst defines vulnerability as the following: "an identifiably increased likelihood of incurring additional or greater wrong" (2008, 195). She explicitly restricts this definition to wrongs, "including wrongful harms and the wrongs that we incur when something to which we have a valid claim is denied us. It cannot extend to any additional harm, or any interest more likely to be difficult to protect, because it is not the case that we have a duty to protect all interests from all harms" (196).

References

Anderson, Christopher. 1994. Panel backs pregnant women in trials. *Science* 263 (5151): 1216.

Beauchamp, Tom L., and James F. Childress. 2009. *Principles of biomedical ethics*. New York: Oxford University Press.

Biller-Andorno, Nikola, and Verina Wild. 2003a. Arzneimittelforschung an Schwangeren: Besonderer Schutz—aber kein Ausschluss aus der Forschung. *Deutsches Ärzteblatt* 100 (15): A-970/B-814/C-760.

_____. 2003b. Zwischen Protektion und Protektionismus—medizinethische Überlegungen zur Teilnahme schwangerer Frauen an klinischen Studien. In *Das Kind als Patient*, ed. Claudia Wiesemann, Andrea Dörries, Gabriele Wolfslast, and Alfred Simon, 302–320. Frankfurt am Main: Campus Verlag.

Bobbert, Monika. 2004. Frauenheilkunde und Geburtshilfe. In *Gutachten "Probanden- und Patientenschutz in der medizinischen Forschung*," ed. Monika Bobbert, Uwe B. Brückner, and Hans Lilie, 55–69. Erstellt im Auftrag der Enquête-Kommission "Ethik und Recht der modernen Medizin" des Deutschen Bundestages. http://webarchiv.bundestag.de/archive/2005/0718/parlament/kommissionen/ethik_med/gutachten/gutachten_03_probandenschutz.pdf (accessed 31 May 2011).

Caschetta, Mary Beth, Wendy Chavkin, and Theresa McGovern. 1993. FDA policy on women in drug trials. *The New England Journal of Medicine* 329 (24): 1815–16.

Che Yaakob, Che Anuar, Abdulla Abu Dzarr, Ahmad Amir Ismail, Nik Ahmad Zuky Nik Lah, and Jacqueline J. Ho. 2010. Anticoagulant therapy for deep vein thrombosis (DVT) in pregnancy. *Cochrane Database of Systematic Reviews* 2010 (6): CD007801.

Coleman, Carl H. 2009. Vulnerability as a regulatory category in human subject research. *Journal of Law, Medicine and Ethics* 37 (1): 12–18.

Council for International Organizations of Medical Sciences (CIOMS). 2002. International ethical guidelines for biomedical research involving human subjects. www.cioms.ch/publications/layout_guide2002.pdf (accessed 31 May 2011).

Council of Europe. 2005. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research. CETS No.: 195. http://conventions.coe.int/Treaty/en/Treaties/html/195.htm (accessed 31 May 2011).

Department of Health and Human Services (HHS). 2009. Code of Federal Regulations. Title 45, Part 46. *See* Subpart 46.111 *(vulnerability) and* Subpart 46.204 *(research on pregnant women)*. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.204 (accessed 31 May 2011).

Dorantes, Dianna M., Alan R. Tait, and Norah N. Naughton. 2000. Informed consent for obstetric anesthesia research: Factors that influence parturients' decisions to participate. *Anesthesia and Analgesia* 91 (2): 369–73.

Duden, Barbara. 1994. *Der Frauenleib als öffentlicher Ort. Vom Missbrauch des Begriffs Leben*. Munich: Mabuse-Verlag.

Faden, Ruth, Anne Drapkin Lyerly, and Maggie Little. 2009. A custom drug. *New York Times*. http://www.nytimes.com/2009/05/10/opinion/10faden.html (accessed 31 May 2011).

Food and Drug Administration (FDA). 1977. General considerations for the clinical evaluation of drugs. Publication no. HEW (FDA) 77-3040.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071682.pdf (accessed 31 May 2011).

Goodin, Robert E. 1985. *Protecting the vulnerable: A reanalysis of our social responsibilities*. Chicago: The University of Chicago Press.

Haire, Doris. 2001. FDA approved obstetrics drugs: Their effects on mother and baby. http://nwhalliance.org/FDAAPPROVED.htm (accessed 31 May 2011).

Helsinki Declaration. 2008. WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3/ (accessed 31 May 2011).

Hurst, Samia A. 2008. Vulnerability in research and health care: Describing the elephant in the room? *Bioethics* 22 (4): 191–202.

Imhof, Christiane. 2005. Antibiotika-Therapie in der Schwangerschaft: Teratogene Risiken von Makroliden, Doxycyclin und Cotrimoxazol. Dissertation zur Erlangung des Doktorgrades der Medizin. Universität Ulm. http://vts.uni-ulm.de/doc.asp?id=5696 (accessed 31 May 2011).

Kipnis, Kenneth. 2006. Vulnerability in research subjects: A bioethical taxonomy (research involving human participants V2). Online Ethics Center for Engineering, National Academy of Engineering. www.onlineethics.org/CMS/research/resref/nbacindex/nbachindex/hkipnis.aspx (accessed 31 May 2011).

Langemak, Shari. 2009. Schwangere Frauen im Impf-Dilemma. In *Welt Online Wissen*. http://www.welt.de/wissenschaft/article4308619/Schwangere-Frauen-im-Impf-Dilemma.html (accessed 31 May 2011).

Lenz, Wolfgang, Rudolf A. Pfeiffer, Wilhelm Kosenow, and D. J. Hayman. 1962. Thalidomide and congenital abnormalities. Letter to the editor. *The Lancet* 279 (7219): 45–46.

Levine, Carol, Ruth Faden, Christine Grady, Dale E. Hammerschmidt, Lisa Eckenwiler, and Jeremy

Sugarman. 2004. The limitations of "vulnerability" as a protection for human research participants. Consortium to examine clinical research ethics. *American Journal of Bioethics* 4 (3): 44–9.

Little, Margaret Olivia, Anne Drapkin Lyerly, and Ruth R. Faden. 2009. Pregnant women & medical research: a moral imperative. *Bioethica Forum* 2 (2): 60–65.

Luna, Florencia. 2009. Elucidating the concept of vulnerability: Layers not labels. *International Journal of Feminist Approaches to Bioethics* 2 (1): 122–39.

Lyerly, Anne Drapkin, Maggie Little, and Ruth Faden. 2008. The second wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches to Bioethics* 1 (2): 5–22.

Lyerly, Anne Drapkin, Maggie Little, and Ruth Faden. 2009. Pregnancy is no time to refuse a flu shot. *New York Times*, September 28. http://www.nytimes.com/2009/09/29/health/views/29essa.html (accessed 31 May 2011).

Mackenzie, Catriona. 1992. Abortion and embodiment. *Australasian Journal of Philosophy* 70 (2): 136–55.

Macklin, Ruth. 1994. Reversing the presumption: The IOM report on women in health research. *Journal of the American Medical Women's Association* 49 (4): 13–16, 21.

Marquardt, Ernst. 1994. Die Contergankatastrophe 1961—Schock und erste Reaktionen. In *Contergan—30 Jahre danach*, ed. Fritz U. Niethard, 79–84. Stuttgart: Enke.

Mastroianni, Anna C., Ruth Faden, and Daniel Federman. 1994. *Women and health research: Ethical and legal issues of including women in clinical studies*. Washington DC: National Academy Press.

Matthews, Anne, Therese Dowswell, David M. Haas, Mary Doyle, and Donal P. O'Mathúna. 2010. Interventions for nausea and vomiting in early pregnancy. Cochrane Database of Systematic Reviews 2010 (9): CD007575.

McBride, William Griffith. 1961. Thalidomide and congenital abnormalities. Letter to the editor. *The Lancet* 278 (7216): 1358.

Meredith, Sheena. 2005. *Policing pregnancy. The law and ethics of obstetric conflict*. Burlington/Aldershot: Ashgate.

Merkatz, Ruth B., Robert Temple, Solomon Sobel, Karyn Feiden, David A. Kessler, and the Working Group on Women in Clinical Trials. 1993. Women in clinical trials of new drugs. A change in Food and Drug Administration policy. *The New England Journal of Medicine* 329 (4): 292–96.

Mohanna, Kay. 1997. Informed consent. Research in pregnancy brings special considerations. *British Medical Journal (Clinical research ed.)* 315 (7102): 249–50.

Müller-Oerlinghausen, Bruno. 2005. Die Rolle der Ärzteschaft bei der Aufklärung der Contergannebenwirkungen und die Auswirkung auf die deutsche Arzneimittelgesetzgebung. In *Die Contergankatastrophe—Eine Bilanz nach 40 Jahren*, ed. Ludwig Zichner, Michael A. Rauschmann, and Klaus-Dieter Thomann. Darmstadt: Steinkopff Verlag.

Nilsson, Lennart. 1965. *Ett barn blir till* [*A child is born*]. Stockholm: Albert Bonniers förlag/Bonnier Fakta.

Paul-Ehrlich-Institut. 2009. Fachliche Information für Ärzte und Apotheker: Pandemie-Impfstoffe in der Schwangerschaft. http://www.pei.de/cln_227/nn_2073016/DE/infos/fachkreise/archiv-sicherheitsinformationen/archiv-infos-influenza-pandemie-2009-2010/schwangerschaft-04-09-2009-pandemie-impfstoffe.html (accessed 1 June 2012).

Rodger, Marc A., Dimitri Makropoulos, Mark Walker, Erin Keely, Alan Karovitch, and Philip S. Wells. 2003. Participation of pregnant women in clinical trials: Will they participate and why? *American Journal of Perinatology* 20 (2): 69–76.

Ruof, Mary C. 2004. Vulnerability, vulnerable populations, and policy. *Kennedy Institute of Ethics Journal* 14 (4): 411–25.

Schaefer, Christof, Horst Spielmann, and Klaus Vetter. 2004. Liberalisierung nicht erforderlich. *Deutsches Ärzteblatt* 101 (4): A165–66.

Schindele, Eva. 1990. *Gläserne Gebär-Mütter: Vorgeburtliche Diagnostik—Fluch oder Segen.* Frankfurt am Main: Fischer Verlag.

Schneider, Ingrid. 1995. *Föten—Der neue medizinische Rohstoff*. Frankfurt am Main: Campus Verlag.

Scott, Amy A., and Dilip M. Purohit. 1989. Neonatal renal failure: a complication of maternal antihypertensive therapy. *American Journal of Obstetrics and Gynecology* 160 (5): 1223–24.

Sherwin, Susan. 1998. Abortion through a feminist ethics lens. In *Ethical theory: A concise anthology,* ed. Heimir Geirsson and Margaret R. Holmgren. Peterborough, Ont.: Broadview Press.

Stormer, Nathan. 2003. Seeing the fetus: The role of technology and image in the maternal–fetal relationship. *JAMA: The Journal of the American Medical Association* 289: 1700.

Vazquez, Juan C., and Edgardo Abalos. 2011. Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database of Systematic Reviews* 2011 (1): CD002256.

Wiesemann, Claudia. 2006. *Von der Verantwortung, ein Kind zu bekommen—Eine Ethik der Elternschaft*. Munich: C.H. Beck Verlag.

Wild, Verina. 2010. *Arzneimittelforschung an schwangeren Frauen. Dilemma, Kontroversen und ethische Diskussion*. Frankfurt am Main: Campus Verlag.

Wilson, James G. 1979. The evolution of teratological testing. *Teratology* 20 (2): 205–211.

Winkelheide, Martin. 2009. Schutz auf dem Prüfstand. Deutschlandfunk—Wissenschaft im Brennpunkt. http://www.dradio.de/dlf/sendungen/wib/1025132/ (accessed 31 May 2011).